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| 08/478,748 | 06/07/95 | WALDMANN T | 2026-4003US3 |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 08/478,748 | Applicant(s) Waldmann |
|---|---|---|
| | Examiner GAMBEL | Group Art Unit 1642 |

☒ Responsive to communication(s) filed on *Mar 27, 1998* .

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-18 and 24-26* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-18 and 24-26* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

1. The location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1642, Technology Center 1600.

2. Applicant's after final amendment, filed 3/27/98 (Paper No. 19) has been entered.
Claims 19-23 have been canceled.
Claim 1 has been amended.
Claim 26 has been added.

Claims 1-18 and 24-26 are pending and being acted upon presently.

3. The text of those sections of Title 35 USC not included in this Action can be found in prior Actions.
This Office Action will be in response to applicant's arguments, filed 3/27/98 (Paper No. 19).
The rejections of record can be found in the previous Office Actions (Paper Nos. 7/9/12/17).

4. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see form PTO-948 previously sent in Paper No. 7. Applicant is reminded to change the Brief Description of the Drawings in accordance with these changes (see 7. Views).

5. The priority date of the instant claimed limitations drawn to ratio such that 25 to 75% saturation of IL-2 receptors is that of the instant application, that is, 6/7/95.

6. The following are the outstanding rejections of record as they apply to the instant claims.

A) Claims 1-14, 16, 17, 24, 25 and newly added claim 26 are rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Ann. Oncol., 1994; 1449, #1) for the reasons of record (Paper Nos. 7/ 9/12/17).

B) Claims 1-14, 16, 17, 24, 25 and newly added claim 26 are rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Important Adv. Oncol., 1994) for the reasons of record (Paper Nos. 7/9/12/17).

C) Claims 1-14, 16, 17, 24, 25 and newly added claim 26 are rejected under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over Waldmann (Leukemia, 1993) for the reasons of record (Paper Nos. 7/ 9/12/17).

D) Claims 1-14 and 24, 25 and newly added claim 26 are rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconjugate Chem., 1993) for the reasons of record (Paper Nos. 7/9/12/17)

E) Claim 15 is rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconjugate Chem., 1993) as applied to claims 1-14 and 16-18, 24, 25 and newly added claim 26 above and in further view of Parenteau et al. (Transplantation et al.) for the reasons of record (Paper Nos. 7/9/12/17).

F) Claims 24-25 are rejected under 35 U.S.C. § 103 as being unpatentable over Kozak et al. (PNAS, 1986) or Diamantstein et al. (Immunol. Rev., 1986) in view of Order et al. (Int. J. Radiat. Oncol. Biol. Phys., 1986) or Wessels et al. (Med. Phys., 1984) for the reasons of record (Paper Nos. 7/9/12/17).

With respect to the clarification of claims 25 and 26; the copy of the Office Action (Paper No. 17) in the instant application indicates that claims 24 and 25 were rejected under 103

G) In view that applicant may have intended to incorporate limitations that set forth discrete method steps to monitor soluble IL-2 receptor levels; the following rejection was set forth in the last Office Action (Paper No. 17). It is noted that applicant's arguments, filed 3/27/98 (Paper No. 19), appear to argue discrete methods steps as they apply to the prior art rejections in view of the instant claims. As pointed out below, the instant claims do not require discrete method steps, provided that the amount of conjugated anti-Tac antibody achieve the claimed saturation levels. Alternatively, such determinations would have been obvious at the time the invention was made.

Claims 1-14 and 16-18, 24, 25 and newly added claim 26 are rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993) and Kreitman et al. (Bioconjugate Chem., 1993) for the reasons of record (Paper Nos. 7/9/12/17) and further in view of art known methods to monitor soluble IL-2 receptors, as evidenced by Rubin et al. (Ann. Intern. Med., 1990) for the reasons of record (Paper No. 17).

And claim 15 is rejected under 35 U.S.C. § 103 as being unpatentable over Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) in view of Hakimi (J. Immunol., 1991), Waldmann et al. (Blood, 1993), Kreitman et al. (Bioconjugate Chem., 1993) and Rubin et al. (Ann. Intern. Med., 1990) as applied to claims 1-14 and 16-18, 24, 25 and newly added claim 26 above and in further view of Parenteau et al. (Transplantation et al.) for the reasons of record (Paper Nos. 7/ 9/12/17).

H) Claims 1-25 and newly added claim 26 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims (1-5, 13, 22 and 28) of copending application Serial No. 07/879,056 in view of Waldmann (Ann. Oncol., 1994; 1449, #1) or Waldmann et al. (Important Adv. Oncol., 1994) or Waldmann (Leukemia, 1993) for the reasons of record (Paper Nos. 7/9/12/17).

Should the claims of copending USSN 07/879,056 be allowed, a terminal disclaimed will be filed at that time. See applicant's amendment, filed 12/6/97 (Paper No. 8),

8. Applicant's arguments, filed 3/27/98 (Paper No. 19), have been fully considered but are not found convincing for the reasons of record.

Applicant asserts that the claimed invention is drawn to a patient a specific a ratio of conjugated to unconjugated anti-Tac such that 25-75% of the IL-2 receptors are saturated. Applicant further asserts that the instant specification set forth a specific algorithm for calculating a proper ratio of conjugated to unconjugated anti-Tac based on a patient's total soluble IL-R levels and relies upon different dosages for patients based upon circulating sIL-2R (see Example 16). It is not entirely clear as to what is the nature of applicant's asserted reliance upon an algorithm in Example 16. It appears that the instant disclosure and newly added claim 26 simply address providing different dosages of radiolabeled anti-Tac based upon sIL-2R levels. As disclosed in the specification as filed (page 52, lines 6-14); the levels of anti-Tac are those estimated to yield binding of radiolabeled anti-Tac to all circulating Tac-expressing tumor cells and to produce approximately 25 to 75% saturation of the IL-2 receptors. These calculations are made on the basis of the observations during the Phase I trial, where binding was assessed by FACS analysis and by binding to the circulating cell of the $^{111}$In-anti-Tac to co-administered with $^{90}$Y-anti-Tac". Similarly, page 13, paragraph 5 of the instant specification discloses that "based on in vivo pharmacokinetic and bioavailability studies during the Phase I trial using $^{90}$Y-anti-Tac, we developed an algorithm to predict a dose of total anti-Tac (sum in mg of unlabeled and labeled antibody) that was sufficient to overcome the effect of soluble antigen levels (i.e., sIL-2R),without excessively diluting antibody-specific activity (see Example 17). Here on page 13 as well as Example 17 disclose the appropriate dosages in the context of sIL-2R levels and that the dosages were based on known toxicity and safety parameters.

Applicant argues that the amount of radiation (e.g. 5-15mCi $^{90}$Y) does not affect the percentage of antibodies being delivered to the target tumor cells and therefore knowledge of this parameter alone is insufficient to determine the proper effective dosages for human treatment. Applicant argues that specific ratio based upon soluble IL-2R levels must be determined for the claimed invention to be practiced.

Applicant asserts that it would not have been obvious to conduct bioavailability analysis to achieve saturation of IL-2 receptors to overcome the effect of soluble IL-2R without diluting antibody specific activity.

With respect to 102/103 rejections of record, the following is noted.

Applicant argues that Waldmann (Ann. Oncol.) fails to teach or suggest is what doses of cytotoxic agent conjugates are administered, the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered and the saturation level of the IL-2 receptors required for effective treatment. Applicant argues that Waldmann fails to meet all of the limitations of the claims that must be met and that the instant claims are drawn to treating a disease using a ratio of conjugated to unconjugated anti-Tac antibodies such that 25-75% of IL-2 receptors are saturated. Applicant asserts that Waldmann (Ann. Oncol.) does not teach or suggest the use of an anti-Tc conjugate with the specific activity of specific doses claimed and as such does to anticipate or render obvious the claimed invention.

Applicant acknowledges that Waldmann (Imp. Adv. Oncol.) Discloses bifunctional antibodies (antibodies conjugated to immunotoxins and to radionuclides), including the use of 5-15 mCi $^{90}$Y. Applicant asserts that this reference does not teach what doses of cytotoxic agent conjugates are administered, the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered and the saturation level of the IL-2 receptors required for effective treatment.

Applicant argues that Waldmann (Leukemia) discloses humanized anti-Tac conjugated to either cytotoxic agents or radionuclides, including the use of 5-15 mCi $^{90}Y$. Applicant asserts that this reference does not teach what doses of cytotoxic agent conjugates are administered, the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered and the saturation level of the IL-2 receptors required for effective treatment.

Applicant argues that the three Waldmann references do not teach using a specific ratio of conjugated to unconjugated anti-Tac producing a saturation level of 25-75% of the IL-2 receptors and that the references do not teach or suggest the use of an anti-Tac conjugate with the specific activity or specific doses claimed.

With respect to the 103 rejections, the following is noted.

Applicant asserts that the combination of the three Waldmann references do not teach what doses of cytotoxic agent conjugates are administered, the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered and the saturation level of the IL-2 receptors required for effective treatment.

Applicant acknowledges that Hakimi et al. teaches humanized anti-Tac, methods for making anti-Tac conjugates and pharmacokinetics in monkeys, but does teach or suggest conjugated antibodies or methods of human treatment using anti-Tac conjugates.

Applicant acknowledges that Kreiman et al. Merely discloses cloning and expression of anti-Tac-Pseudomonas exototoxin fusions and toxicity studies but is silent on methods of human treatment using anti-Tac conjugates.

Applicant acknowledges that Parenteau et a. discloses conjugated anti-Tac for graft prolongation in conjunction with G-CSF treatment, but does ot teach or suggest a ratio of conjugated to nonconjugated anti-Tac as taught by the claimed invention or the use of soluble IL-2 receptor levels.

With respect to the clarification of claims 25 and 26; the copy of the Office Action (Paper No. 17) in the instant application indicates that claims 24 and 25 were rejected under 103

Applicant acknowledges that Kozak et al. teaches methods of making effective anti-Tac conjugates; that Diamantstein et al. Discloses the IL-2 receptor and unconjugated anti-Tac treatment of GVHD; and that Order et al. Discloses conjugated anti-ferritin in conjunction with the use of external radiation to increase antibody uptake. However applicant argues that these secondary references do not teach or suggest what doses of cytotoxic agent conjugates are administered, the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered and the saturation level of the IL-2 receptors required for effective treatment.

Applicant argues that Wessels et al. discloses a theoretical study which teaches away from the claimed invention. For example, pages 641-642 discloses that tumor associated antibodies labeled with radionuclides intended for a radiation therapy application require a high specific radiolabel. Applicant argues that this directs the skilled artisan to obtain the highest specific activity (i.e. all conjugated anti-Tac with no unconjugated anti-Tac) is necessary for proper therapy, while the instant invention encompasses a lower specific activity is necessary to attain a therapeutic effect without excessive toxicity and that the

proper dosage is based upon a patient's sIL-2R levels. In addition, applicant argues that this reference does not teach or suggest what doses of cytotoxic agent conjugates are administered, the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered and the saturation level of the IL-2 receptors required for effective treatment.

Applicant acknowledges that Rubin et al. describe clinical applications of sIL-2R for diagnosis and are related to measuring disease activity, response to therapy and prognosis in conditions associated with T/B cell immune activation. Applicant asserts that there is no teaching or suggestion that sIL-2R levels can be used to calculate effective dosing for the treatment of disease. In addition, applicant argues that this reference does not teach or suggest what doses of cytotoxic agent conjugates are administered, the ratio of radionuclide-conjugated to nonconjugated anti-Tac administered and the saturation level of the IL-2 receptors required for effective treatment.

Applicant's arguments are not found convincing essentially for the reasons of record and addressed herein. Again, it is noted that the prior art, which is applicant's own work, relies upon employing the same or nearly the same anti-Tac antibody at dosages of antibody and radioactivity for the same purposes, including the same or similar clinical trials, as encompassed by the claimed invention. Applicant's assertions in the absence of objective evidence do not obviate that the claimed limitations are encompassed by the use of the same anti-Tac antibodies at the disclosed dosages and radionuclide activity in the same patient populations, as taught by the prior art. Applicant's reliance on the ratio of radionuclide-conjugated to non-conjugated anti-Tac antibodies is not found convincing; since for the most part, the claims simply require a certain range of activity of radionuclide for a certain range of an amount of antibody and that such dosages are the same or nearly the same as the prior art either under anticipation or obviousness. Applicant reliance on the saturation level of the IL-2 receptors is not found convincing; since for the most part, the claims simply require that the amount of radionuclide conjugated anti-Tac antibody achieve a certain level of saturation in a range of IL-2R saturation or that it is administered to patients having a certain range of sIL-2R. Applicant's arguments appear to rely, in part, on methods of making radioimmunoconjugates or measuring IL-2R saturation or sIL-2R levels. On one hand, such limitations are not required by the claimed methods, since the claims are met by using an amount of anti-Tac conjugated to a radionuclide within the claimed range and which the prior art does teach. On the other hand, applicant's arguments appear to rely upon art known methods to make radioimmunoconjugates at desired or known levels of activity or appear to rely upon such methods of making and determination that was known and taught by the prior art of record.

As pointed out previously, Waldmann (Ann. Oncol.), which is authored by applicant, clearly teaches the use of same 5-15 mCi $^{90}$Y-labeled anti-Tac antibody in Phase I and Phase II trials (page 16, column 1 paragraph 2). The range of 2-100 mg of anti-Tac antibody provided with 5-15 mCi $^{90}$Y-labeled anti-Tac antibody recited in the claims is a broad range as well as 25-75% saturation of total IL-2 receptors and surely would have been encompassed by the use of the same 5-15 mCi $^{90}$Y-labeled anti-Tac antibody disclosed in the prior art. Applicant has not provided objective evidence to indicate that the prior art teachings do not meet the effective dosages including the saturation of IL-2 receptors encompassed by the claims.

As pointed out previously, Waldmann (Imp. Adv. Oncol.), which is authored by applicant, appears to teach the use of same 5-15 mCi $^{90}$Y-labeled anti-Tac antibody disclosed in Waldmann (Leukemia, 1993, cited as reference 22 in Waldmann, Important Adv. Oncol., 1994 and of record in the instant application, see 892 and the next section)(see page S154, column 1 or Leukemia, 1993) and which appears to be the same recitation of Waldmann (Ann. Oncol., 1994; page 16, column 1 paragraph 2) relied upon above in the previous section. Therefore, the reference disclosure of 5-15 $\mu$Ci of $^{90}$Y-labeled anti-Tac antibody appears to be a mistake and should be 5-15 mCi $^{90}$Y-labeled anti-Tac antibody, as the reference clearly indicates by its own citation as well as by applicant himself. The range of 2-100 mg of anti-Tac antibody provided with 5-15 mCi $^{90}$Y-labeled anti-Tac antibody recited in the claims is a broad range as well as 25-75% saturation of total IL-2 receptors and surely would have been encompassed by the use of the same 5-15 mCi $^{90}$Y-labeled anti-Tac antibody disclosed in the prior art. Applicant has not provided objective evidence to indicate that the prior art teachings do not meet the effective dosages including the saturation of IL-2 receptors encompassed by the claims.

As pointed out previously, Waldmann (Leukemia), which is authored by applicant, appears to teach the use of 5-15 mCi $^{90}$Y-labeled anti-Tac antibody d for the treatment of HTLV-1-associated Tac-expressing ATL, thereby providing therapeutic effect (see page S154, column 1). The range of 2-100 mg of anti-Tac antibody provided with 5-15 mCi $^{90}$Y-labeled anti-Tac antibody recited in the claims is a broad range as well as 25-75% saturation of total IL-2 receptors and surely would have been encompassed by the use of the same 5-15 mCi $^{90}$Y-labeled anti-Tac antibody disclosed in the prior art. Applicant has not provided objective evidence to indicate that the prior art teachings do not meet the effective dosages including the saturation of IL-2 receptors encompassed by the claims.

The primary prior art teachings of these Waldmann references clearly indicate that the use of anti-Tac antibody radionuclide (and cytotoxin) conjugates were known and used at the time the invention was made and that these dosages are encompassed by the instant claimed limitations.

Again and in addition, applicant argues the references individually and not their combination.

Applicant is reminded that instant claims 24-25 are drawn to pharmaceutical compositions and not methods. The combined references of record clearly provide motivation to conjugated anti-Tac antibodies with various conjugates including a β-emitting isotope such as $^{90}$Yttrium as a radio-immunotherapeutic reagent for the reasons of record to eliminate unwanted Tac positive cells observed in a number of T-cell mediated disorders in humans.

The range of 2-100 mg of anti-Tac antibody provided with 5-15 mCi $^{90}$Y-labeled anti-Tac antibody recited in the claims is a broad range as well as 25-75% saturation of total IL-2 receptors and surely would have been encompassed by the use of the same anti-Tac conjugated antibodies disclosed in the prior art. Applicant has not provided objective evidence to indicate that the prior art teachings do not meet the effective dosages including the saturation of IL-2 receptors encompassed by the claims.

Applicant argues that the examiner has not provided any basis that it would have been obvious to conduct bioavailability analysis to achieve saturation of IL-2 receptors to overcome the effect of soluble IL-2R without diluting antibody specific activity. It is clear that the prior art of record teach the use of conjugated anti-Tac antibodies to target certain diseases, wherein said diseases encompass elevated levels of IL-2R. It is clear that the prior art of record teach pharmacokinetic studies to achieve desired therapeutic goals. In contrast to applicant's assertions, bioavailability is a critical parameter of pharmacokinetic studies, including Phase I trials, as evidenced by the Merck Manual 16th Edition, pages 2610-2613).

As pointed out previously, the prior art of record does not disclose generating effective doses that achieve 25-75% saturation of IL-2 receptors per se. However, it was art known and routinely practiced to monitor soluble IL-2 receptors in various disease states at the time the invention was made, as evidence by Rubin et al. (see entire document). Rubin also discloses that such information would be useful in monitoring the efficacy and management of therapeutic treatment.

Also, the Waldmann review articles all disclose the association of IL-2 receptors and various diseases encompassed by the claimed invention as well as it was important to maintain the activity levels of anti-Tac antibody therapies in treating such diseases (see entire documents). The combined references of record also address the importance of pharmacokinetic analyses. Therefore, it would have been obvious to one of ordinary skill in the art to select for appropriate ratios of anti-Tac antibody and conjugate ratios as well as the level of saturation in vivo to achieve therapeutic efficacy in the face of soluble IL-2 receptors in patients. It would have been recognized that there would have been a range of therapeutic doses since differences in the nature of diseases as well as individual patients were known and expected in the art at the time the invention was made. Also, the combined references clearly taught efficacy of anti-Tac antibody conjugate therapies including human patients, therefore, it would have been obvious to establish parameters or calculations associated with antibody-conjugate ratios as well as saturation levels based upon such therapeutic successes and pharmacokinetic studies. Therefore, it would have been obvious to establish via pharmacokinetic studies as well as clinical trials bioavailability information to predict a dose of total anti-Tac antibody conjugates that was sufficient to overcome the effect of soluble IL-2 receptor levels without diminishing antibody specific activity. This would have resulted in the effective dosages encompassed by the claimed limitations, including ratios of anti-Tac to conjugates as well as IL-2 receptor saturation levels

As indicated of record, the references clearly teach the same amount or nearly the same amount of anti-Tac antibody conjugates for the same methods by the same person as that presently claimed. Applicant has not provided sufficient objective evidence to distinguish between the amount of anti-Tac antibody conjugates taught or known by virtue of the combined references differs from that presently claimed. The claimed effective dosages are either taught by the references or it would have obvious to one of ordinary skill in the art at the time the invention was made to provide dosages encompassed by the claimed methods and compositions in meeting the needs of either reducing or eliminating measurable or assessable disease. Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to determine and establish the parameters including antibody-conjugate ratios and IL-2 receptor saturation associated with anti-Tac antibody conjugate efficacy in various therapeutic modalities. From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention was a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Therefore, applicant's arguments are not found persuasive and the rejection is maintained.

9. Claims 1-18 and 24-25 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are indefinite in their recitations of "said ratio based upon soluble IL-2 receptor levels, such that 25 to 75% saturation of total IL-2 receptors is provided" (recited in claim 1) or "wherein the effective dose is provided in a ratio of anti-Tac to cytotoxin-conjugate, said ratio sufficient to produce 25 to 75% saturation of IL-2 receptors by said cytotoxin conjugate" (recited in claim 24) because it is unclear whether these limitations are properties of effective dosages already claimed or whether these limitations are drawn to discrete and additional method steps.

The amendments must be supported by the specification so as not to add any new matter.

Applicant's arguments, filed have ben fully considered but are not found convincing. Applicant argues that the limitations in question are an important aspect of determining and thus providing an effective dosage. Also, it appears that applicant relies upon certain method steps disclosed in the specification. However, the claims as recited do not necessarily require discrete method steps. In view of applicant's arguments, the claims remain ambiguous as to whether applicant is relying upon or not relying upon discrete method steps as they apply to the instant claims. Applicant is reminded that the claims are read in light of the specification, but the limitations of the specification are not read into the claims.

Applicant's arguments are not found persuasive.

10. No claim is allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Since the fee set forth in 37 CFR 1.17(r) for a first submission subsequent to a final rejection has been previously paid, applicant, under 37 CFR 1.129(a), is entitled to have a second submission entered and considered on the merits if, prior to abandonment, the second submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a second submission and the appropriate fee of $ for a entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. If a notice of appeal and the appeal fee set forth in 37 CFR 1.17(e) were filed prior to or with the payment of the fee set forth in 37 CFR 1.17(r), the payment of the fee set forth in 37 CFR 1.17(r) by applicant will be construed as a request to dismiss the appeal and to continue prosecution under 37 CFR 1.129(a). In view of 35 U.S.C. 132, no amendment considered as a

result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to **[lila.feisee@uspto.gov]**.

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
Patent Examiner
Technology Center 1600
June 17, 1998

LILA FEISEE
SUPERVISORY PATENT EXAMINER